Basic and Translational Investigations

Efficacy of the HSP90 inhibitor 17-AAG in human glioma cell lines and tumorigenic glioma stem cells

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Abstract

Glioblastoma multiforme (GBM) arises from genetic and signaling abnormalities in...
components of signal transduction pathways involved in proliferation, survival, and the cell cycle axis. Studies to date with single-agent targeted molecular therapy have revealed only modest effects in attenuating the growth of these tumors, suggesting that targeting multiple aberrant pathways may be more beneficial. Heat shock protein 90 (HSP90) is a molecular chaperone that is involved in the conformational maturation of a defined group of client proteins, many of which are deregulated in GBM. 17-allylamino-17-demethoxygeldanamycin (17-AAG) is a well-characterized HSP90 inhibitor that should be able to target many of the aberrant signal transduction pathways in GBM. We assessed the ability of 17-AAG to inhibit the growth of glioma cell lines and glioma stem cells both in vitro and in vivo, as well as assessing its ability to synergize with radiation and/or temozolomide, the standard therapies for GBM. Our results reveal that 17-AAG is able to inhibit the growth of both human glioma cell lines and glioma stem cells in vitro, and is able to target the appropriate proteins within these cells. In addition, 17-AAG can inhibit the growth of intracranial tumors, and can synergize with radiation both in tissue culture and in intracranial tumors. This compound was not found to synergize with temozolomide in any of our models of gliomas. Our results suggest that HSP90 inhibitors like 17-AAG may have therapeutic potential in GBM, either as a single agent or in combination with radiation.

**Key Words:** 17-AAG, gliomas, stem cells, radiosensitizer